indefiniteness, and over the prior art. Based on the changes to the claims made above and the comments made here, the applicants respectfully request the Examiner to again reconsider the merits of this patent application.

Rejection to Claim 18 under §112

The Examiner rejected claim 18 due to lack of specificity in identifying the particular native sequence. That deficiency has now been cured by reference to the specific source strain of Bacillus thuringiensis.

First Rejection under §112 for Lack of Enablement

The Examiner, in the Office Action, rejected all the claims in the parent patent application on the grounds that the specification of this application is not enabling. This rejection was premised on the fact that there may substantial variation in codon usage tables. In response to the Examiner's suggestion, the applicants have adopted the language suggested by the Examiner to cure this issue. However, the applicants would assert that, in spite of minor differences in codon preference listed in different tables, that such tables of codon usage, is tabulated appropriately, will have substantial similarity and equivalence to the table of Fig. 1.

Second Rejection to Specification and Claims for Lack of Enablement

The Examiner is continues to apply an incorrect legal standard to this application in making this rejection. The evidence in the specification does demonstrate that the applicants invention works better than the prior art. However, even if the evidence did not support his conclusion, that alone would not make the specification non-enabling. The specification clearly enables the creation of the gene sequences, plants and the method claimed by the above claims.

The Examiner continues to argue that the applicants have not demonstrated with sufficient certainty that the synthetic genes described here kill insects better than the native genes. The Examiner continues to question the applicants' method of scoring the transgenic plants for relative insect toxicity. The applicants continue to insist that, regardless of the method of scoring relative plant toxicity, the invention is enabled.

To meet the requirements of §112, first paragraph, the specification must teach how to use the invention. The specification here teaches a method of making altered nucleotide sequences and the specification contains a table of preferred codon usage for use in such sequences, and provides instructions and guidance on how to construct a synthetic sequence from the information on the table. The Examiner does not dispute that, but asserts the specification is non-enabling by arguing that the evidence is not persuasive that the applicants' synthetic sequences are better than the prior art native sequences. That argument is perhaps relevant to unobviousness, but not to enablement. It is not a requirement of §112 that the invention be better, just that it be defined and enabled.

The Examiner has, in essence, repeatedly doubted the scientific data showing that the applicants altered codon gene functions any better that the native gene. To help the Examiner be satisfied on this point, two recent papers are submitted herewith. Perlak et al. Proc. Natl Acad Sci USA, 88:3324-3328 (1991), and Koziel et al. Bio/Technology, 11:194-299 (1993). Neither of these papers is, of course, prior art. The papers are submitted simply to demonstrate a scientific fact. The fact is that for expressing the B.t. gene in plants, if one constructs an artificial sequence with altered codons, to as to have a greater C-G content in the coding sequence, the gene expresses better in transgenic plants. See, the Perlak et al. paper pp 3324-3325, and Koziel et al. at 194-195. Note that use of the codon usage table of Fig. 1 has the net effect of replacing A-T content with greater C-G content in a gene. For all codons on the table, except for the weakly favored proline codons, the favored codons all have a C or G at the third base pair position. As both Perlak and Koziel report, the change in nucleotide content from A-T to C-G results in better expression of the B.t. protein. Note that the specification of this application makes in clear that the fundamental change in nucleotide usage created in a gene altered in accordance with this invention is to increase C-G content at the expense of A-T content (specification page 10, line 32 to page 11 line 2). Although the methodology for the substitution is slightly different in this case from the method described in the Perlak et al. approach, the overall modifications to the gene sequence, and the outcome and effect on expression, are quite similar.

These two documents are submitted to establish for the benefit of the Examiner that there is independent scientific evidence establishing the

efficacy of the strategy set forth in the present patent application. While the applicants continue to belief that their teaching is sufficient to establish efficacy, the Examiner now also has independent evidence establishing the same efficacy. This should be persuasive that the method taught by the applicants here is genuinely effective to increase gene expression. Hence, this ground of rejection is misplaced.

Second Rejection under §112 for Overbreadth

The Examiner also found the claims overbroad as to size of B.t. toxin and suggested language to overcome this rejection. The applicants have adopted the suggested language, and this rejection should now be obviated.

Rejection under §103 over Prior Art

The Examiner also continues to reject the claims of the present application over a combination of seven prior art references. Again, the applicants respectfully disagree.

It is still true that no reference is cited which shows taking a gene which expresses poorly and changing only the codon usage to achieve better expression. The applicants have repeatedly pointed out that Hoekema's observation that a highly expressed gene can be altered to express less efficiently does not assure that a poorly expressed gene can be made to express better merely by changing codon usage.

The Examiner asserts, in essence, that since the B.t. gene was known to express poorly in plants, and since it was known to have a sequence rich in A-T content, and since plant codon usage tables show plants preferred C-G content, that it would have been obvious to alter the native gene sequence to achieve enhanced expression. The applicants have argued that it might be obvious to try that approach, but that there was insufficient guidance in the prior art to provide any assurance that the approach would actually work to enhance expression of the toxin protein. The Examiner responded in the Office Action by again questioning the applicants' data as to increased level of expression.

The Examiner should be satisfied from the new papers supplied herewith that the claimed increase in expression level is real. All the experimenters in this field have now reach essentially the same conclusion, that the altered codon gene works better than the native one.

Now that it is established that the altered gene does improved efficiency of expression, the Examiner's analysis fails. Nothing in the cited combination of references provides any reasonable assurance or expectation that this strategy would actually work to increase expression of the toxin protein in plants, yet it does work. Without the reasonable expectation of success, this is simply an inappropriate "obvious to try" rejection.

Finally, the Examiner continues to be overly concerned about the applicants' data on Table 1. The applicants continue to assert that convincing data is presented there. If one compares the native B.t. sequence in pTVAMVBTSH with the substituted sequence in pTVAMVBT4, one sees that the distribution of expressing plants was quite different, whatever the criteria in establishing the difference between the rating classes. This is the same effect noted by the other investigators in this field.

The Examiner stated in the Office Action, toward the end of this rejection, that the claimed invention is not distinguished from the prior art. However, the fact is that the method, the gene sequence, and the plants described here are all clearly distinguished from the prior art, i.e. the native B.t. sequence, by the express language of the claims. No reference shows such a codon substitution strategy for a gene in a foreign host. The question is not whether the claims are distinguished over the art, which they clearly are, but whether they are unobvious over it.

In summary, the applicants have described and claimed a strategy for increasing expression of a protein which has been difficult to express in plants. The data in this application, and the research results from other groups, establish that the strategy is a successful one. The strategy is unprecedented. The Examiner has assembled a set of seven references, yet none provides any suggestion that the strategy of the applicants would actually work. Only hindsight can find this obvious.

It is again respectfully requested that the Examiner reconsider this rejection, and withdraw it.

Conclusion

Wherefore, again the Examiner is respectfully requested to revisit the merits of the specification and claims of this patent application. An early and favorable reply is solicited. A separate request for extension of time has been submitted so that this response will be considered as timely filed.

Respectfully submitted,

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